Pharmacy Update
November/December 2005

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In This Issue

Fondaparinux Sodium (Arixtra™): A Brief Review

Clinical Pharmacology

Fondaparinux sodium (ORG31540/SR90107A) is a synthetic pentasaccharide that is structurally identical to the antithrombin (AT) binding site of heparin. Despite its name, antithrombin bound to fondaparinux inhibits factor Xa, not thrombin. However, it does inhibit thrombin production.

Fondaparinux can reduce thrombus formation in several animal models.[5,6,8,12-14] In an incision animal model, no more bleeding was observed in fondaparinux-treated animals compared to controls. In contrast, heparin and the low molecular weight heparin fraxiparin were associated with significant blood loss.[5,6]

Fondaparinux has an anti-Factor Xa potency of ~650 IU/mg at pH 8.4 and ~860 IU/mg at pH 7.35.[3] In assays, the anti-Factor Xa activity ranges from 300 units/mg to 4,000 units/mg, with most determinations falling between 600 and 800 units/mg.[3-5,12]

Cross-reactivity was not observed with fondaparinux to antibodies from 49 patients with type II heparin-induced thrombocytopenia.[15] Additional studies are necessary to determine if fondaparinux may be a safe alternative to heparin in patients developing this complication. Product labeling currently recommends fondaparinux be used with caution in patients with a history of heparin-induced thrombocytopenia.[1]

Indications

Fondaparinux is indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and for the prophylaxis of DVT in patients undergoing hip fracture surgery, hip replacement surgery, or knee replacement surgery.[1]

Pharmacokinetics

The bioavailability of fondaparinux is complete following subcutaneous administration (absolute bioavailability is 100 percent).[1,16] Peak concentrations are reached within 2 to 3 hours after subcutaneous administration.[1,16]

Fondaparinux has a linear pharmacokinetic profile.[16] Fondaparinux is distributed primarily in the blood, with a volume of distribution of 7 to 11 L.[1] Fondaparinux is highly bound to antithrombin III and does not bind significantly to other plasma proteins or red blood cells.[1,17] The elimination half-life is 17 to 21 hours.[1,16,18,19]

Renal excretion is the primary route of elimination.[4,19,20] Fondaparinux is primarily eliminated unchanged in the urine in patients with normal renal function.[1] In healthy subjects up to 75 years of age, up to 77 percent of the administered dose is eliminated in the urine unchanged in 72 hours.[1] Decreases in renal function result in increases in the AUC and half-life and decreases in systemic clearance of fondaparinux. The total clearance of fondaparinux is about 25 percent lower in patients with mild renal impairment (CrCl >50 to 80 mL/min), about 40 percent lower in patients with moderate renal impairment (CrCl 30 to 50 mL/min), and about 55 percent lower in patients with severe renal impairment (CrCl <30 mL/min) compared to subjects with normal renal function.[1] The average

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half-life of fondaparinux is 13 hours in individuals with a creatinine clearance of 91 to 140 mL/min, 29 hours with a creatinine clearance of 31 to 60 mL/min, and 72 hours with a creatinine clearance of 10 to 30 mL/min.[20] Fondaparinux clearance is increased approximately 20 percent during hemodialysis.[1]

The clearance of fondaparinux is reduced by about 30 percent in patients weighing less than 50 kg.[1] Fondaparinux elimination is prolonged in patients over 75 years of age. Total clearance of fondaparinux is about 25 percent lower in patients over 75 years of age compared to subjects less than 65 years of age.[1] The pharmacokinetics of fondaparinux are not affected by gender, and do not appear to be influenced by race.[1] The pharmacokinetics of fondaparinux have not been evaluated in patients with hepatic impairment.[1]

Comparative Efficacy

Postoperative DVT Prophylaxis

Fondaparinux was compared with enoxaparin in the prevention of DVT in a double-blind study enrolling 933 patients undergoing total hip replacement. Patients were randomly assigned to postoperative therapy with subcutaneous enoxaparin 30 mg every 12 hours or subcutaneous fondaparinux 0.75 mg, 1.5 mg, 3 mg, 6 mg, or 8 mg once daily. The first fondaparinux injection was administered 6 hours after surgery. The first enoxaparin injection was administered 12 to 24 hours after surgery. Enoxaparin or fondaparinux was administered for a maximum of 10 days or until a predischarge venogram was obtained after a minimum of 5 days. The mean duration of treatment was 6 days in those patients receiving fondaparinux 0.75 mg and 3 mg therapy. The mean duration of treatment was 7 days in those patients treated with fondaparinux 1.5 mg, 6 mg, and 8 mg, and enoxaparin therapy. An adequate efficacy evaluation could be performed for 593 patients included in an intent-to-treat analysis. Rates of venous thromboembolism were 9.4 percent in the enoxaparin group, 11.8 percent for the fondaparinux 0.75 mg group, 6.7 percent for the fondaparinux 1.5 mg group, 1.7 percent for the fondaparinux 3 mg group ($p=0.003$ vs fondaparinux 0.75 mg; $p=0.01$ vs enoxaparin), 4.4 percent for the fondaparinux 6 mg group, and 0 percent for the fondaparinux 8 mg group. Compared to enoxaparin, the risk of venous thromboembolism was reduced by 29 percent (6.7 vs 9.4 percent; $p=0.51$) with fondaparinux 1.5 mg and 82 percent (1.7 vs 9.4 percent; $p=0.01$) with fondaparinux 3 mg. A high incidence of major bleeding episodes was observed in both the 6 mg and 8 mg fondaparinux groups, and enrollment at those dose levels was discontinued early. Rates of bleeding with enoxaparin and the fondaparinux 3 mg dose were similar. The overall rates of major bleeding were 0.5 percent with fondaparinux 1.5 mg, 4.5 percent with fondaparinux 3 mg, 16.7 percent with fondaparinux 6 mg, 17.3 percent with fondaparinux 8 mg, and 3.5 percent with enoxaparin. There were no reports of major bleeding in the patients treated with fondaparinux 0.75 mg.[7] Based on the efficacy and safety results in this study, a dose of 2.5 mg once daily was selected for further studies.[21]

Fondaparinux was also compared with enoxaparin in the prevention of venous thromboembolism after hip fracture (upper third of the femur) surgery in a double-blind study enrolling 1,711 patients. Surgery had to be performed within 48 hours after admission and the hospital admission had to be within 24 hours of the injury. Patients ranged in age from 17 to 101 years (mean age 77 years); 75 percent were female, and 99 percent were Caucasian. Patients with multiple trauma affecting more than one organ system, serum creatinine greater than 2 mg/dL, pregnancy, active bleeding, congenital or acquired bleeding disorders, current ulcerative or angiodysplastic gastrointestinal disease, history of hemorrhagic stroke or brain, spinal, or ophthalmologic surgery within the previous 3 months, planned use of an indwelling intrathecal or epidural catheter for more than 6 hours after surgery, hypersensitivity to heparin, low molecular weight heparins, porcine products, or iodinated contrast medium, contraindications to anticoagulant therapy, addictive behavior, or platelet count less than 100,000/mm^3 were excluded from the study. Patients were randomly assigned prophylaxis with either subcutaneous fondaparinux 2.5 mg once daily starting 6 hours postoperatively or enoxaparin 40 mg once daily starting 12 hours preoperatively. The second dose of all the medications was given 12 hours or more after surgery. Day-1 for the study was the day of surgery. The use of intermittent pneumatic compression, dextran, thrombolytic drugs, anticoagulants, and antiplatelet drugs were prohibited during the evaluation period. Graduated compression stockings and physiotherapy were recommended. Because surgery was delayed, 10.9 percent of patients in the fondaparinux group received their first dose preoperatively. Enoxaparin was given postoperatively (average of 18 hours postoperatively), rather than preoperatively, to 74.7 percent of patients assigned to the enoxaparin group. The clinical impact of this delay in initiating enoxaparin prophylaxis is unclear (results were not compared for patients who initiated enoxaparin preoperatively compared to those initiated postoperatively). Patients were treated for 9 days or until a predischarge venogram was obtained after day-5. The primary efficacy endpoint was venous thromboembolism (documented DVT and/or documented symptomatic pulmonary embolism) up to postoperative day-11. Secondary endpoints included total, proximal, or distal deep-vein thrombosis or symptomatic venous thromboembolism up to day-11 and symptomatic venous thromboembolism up to day-49; the primary safety endpoint was the incidence of major bleeding. Efficacy was assessed in 1,250 patients (73.1 percent); 73.7 percent of those assigned to fondaparinux therapy and 72.4 percent of those assigned to enoxaparin therapy. The median number of injections during the prophylactic therapy was 7 days in both groups. The incidence of venous thromboembolism by day-11 was 8.3 percent (95 percent CI: 6.3, 10.8; 52 of 626 patients) in the fondaparinux group and 19.1 percent (95 percent CI 16.1, 22.4; 119 of 624 patients) in the enoxaparin group ($p<0.001$). A 56.4 percent relative risk reduction in favor of fondaparinux compared with enoxaparin was

observed (95 percent CI, 39 percent to 70.3 percent; p<0.001). The incidence of all DVT was 7.9 percent (95 percent CI 5.9 percent to 10.2 percent) in the fondaparinux group and 18.8 percent (95 percent CI 15.8 percent to 22.1 percent) in the enoxaparin group (p<0.001). The incidence of proximal DVT was 0.9 percent (95 percent CI 0.3 percent to 2 percent) in the fondaparinux group and 4.3 percent (95 percent CI 2.9 percent to 6.2 percent) in the enoxaparin group (p<0.001). The incidence of symptomatic venous thromboembolism was similar in the two groups, as was the incidence of pulmonary embolism (11 patients in each group). Major bleeding occurred with similar frequency in the two groups; minor bleeding occurred more frequently in the fondaparinux group (4.1 percent vs 2.1 percent, p=0.02).[1,22,23]

In another double-blind study enrolling 1,049 patients, fondaparinux and enoxaparin were compared in the prevention of venous thromboembolism after elective major knee surgery (resection of the distal end of the femur or proximal end of the tibia or revision of at least one component of previously implanted total-knee prosthesis). Patients ranged in age from 19 to 94 years (mean age 68 years); 59 percent were women, and 88 percent were Caucasian. Patients with a serum creatinine greater than 2 mg/dL or platelet count less than 100,000/mm^3 were excluded from the study. Patients were also excluded if they had contralateral knee surgery at the same time or within 2 weeks, were pregnant or not using effective contraception, or had an active bleed, congenital or acquired bleeding disorder, current ulcerative or angiodysplastic gastrointestinal disease, hemorrhagic stroke or brain, spinal, or ophthalmologic surgery within the last 3 months, insertion of an indwelling intrathecal or epidural catheter during the treatment period, unusual difficulty in administering epidural or spinal anesthesia, hypersensitivity to heparin, low molecular weight heparins, porcine products, or iodinated contrast medium, a contraindication to anticoagulant therapy, addictive disorder, or required anticoagulant therapy. Patients were treated with either subcutaneous fondaparinux 2.5 mg once daily starting postoperatively 6 hours postoperatively or subcutaneous enoxaparin 30 mg every 12 hours starting 12 to 24 hours postoperatively. Day-1 was defined as the day of surgery. Fondaparinux was initiated 6 hours (mean 6.25 hours) after surgery in 94 percent of patients. Enoxaparin was initiated 12 to 24 hours (mean 21 hours) after surgery in 96 percent of patients. Study drug was continued for 9 days or until a predischarge venogram was obtained after day-5. Dextran and other anticoagulants, fibrinolytic, and antiplatelet drugs were discouraged during the study drug therapy. The primary efficacy endpoint was venous thromboembolism up to postoperative day-11. Secondary endpoints were total, proximal, or distal deep-vein thrombosis or symptomatic venous thromboembolism up to day-11 and symptomatic venous thromboembolism up to day-49. The primary safety endpoint was the incidence of major bleeds. Efficacy evaluation was available for 724 patients (69 percent). Venous thromboembolism up to day-11 occurred in 12.5 percent (95 percent CI: 9.2, 16.3; 45 of 361) in the fondaparinux group and 27.8 percent (95 percent CI: 23.3, 32.7; 101 of 363) in the enoxaparin group (p<0.001). A 55.2 percent relative risk reduction for venous thromboembolism was reported for fondaparinux compared to enoxaparin (95 percent CI, 36.2 percent to 70.2 percent; p<0.001). The incidence of proximal deep-vein thrombosis was reduced by 54.5 percent in the fondaparinux group (p=0.06) and the incidence of distal deep-vein thrombosis was reduced by 55.9 percent (p<0.001). The incidence of pulmonary embolism did not differ between the groups. Major bleeding occurred more frequently in the fondaparinux group (2.1 percent [95 percent CI: 1.1,3.8] vs 0.2 percent [95 percent CI: 0, 1.1]; p=0.0061). The incidence of minor bleeding did not differ between the groups.[1,24,25]

Results of two other large clinical studies were reported in abstracts and the product labeling. Fondaparinux and enoxaparin were compared in the prevention of venous thromboembolism in a double-blind study enrolling 2,275 patients undergoing primary total hip replacement or revision. Patients ranged from 18 to 92 years of age (mean 65 years); 52 percent were women, and 94 percent were Caucasian. Patients with a serum creatinine greater than 2 mg/dL or a platelet count less than 100,000/mm^3 were excluded. Patients were treated with either subcutaneous fondaparinux 2.5 mg once daily or subcutaneous enoxaparin 30 mg every 12 hours. Study drug was initiated postoperatively and continued for 9 days or until a predischarge venogram was obtained after day-5. Efficacy was assessed in 1,585 patients. Fondaparinux was initiated 6 hours (mean 6.5 hours) after surgery in 92 percent of patients. Enoxaparin was initiated 12 to 24 hours (mean 20.25 hours) after surgery in 97 percent of patients. The incidence of venous thromboembolism by day-11 was 6.1 percent (95 percent CI: 4.5, 8; 48 of 787 patients) in the fondaparinux group and 8.3 percent (95 percent CI 6.5, 10.4; 66 of 797 patients) in the enoxaparin group (NS). Although neither the incidence of proximal DVT or symptomatic pulmonary embolism differed in the two treatment groups, the incidence of all DVT was lower in the fondaparinux group (5.6 percent in the fondaparinux group and 8.2 percent in the enoxaparin group [p<0.05]). Bleeding rates were comparable.[1,26]

Fondaparinux and enoxaparin were also compared in the prevention of venous thromboembolism after elective hip replacement surgery in a double-blind study enrolling 2,309 patients. Patients ranged in age from 24 to 97 years (mean age 65 years); 58 percent were women, and 99 percent were Caucasian. Patients with a serum creatinine greater than 2 mg/dL or a platelet count less than 100,000/mm^3 were excluded. Patients were treated with either fondaparinux 2.5 mg once daily subcutaneously starting postoperatively or enoxaparin 40 mg once daily subcutaneously starting preoperatively. Study drug was continued for 9 days or until a predischarge venogram was obtained after day-5. The efficacy analysis included 1,827 patients. Fondaparinux was initiated 6 hours (mean 6.25 hours) after surgery in 86 percent of patients. Enoxaparin was

initiated 12 hours before surgery in 78 percent of patients. The incidence of venous thromboembolism by day-11 was 4.1 percent (95 percent CI: 2.9, 5.6; 37 of 908 patients) in the fondaparinux group and 9.2 percent (95 percent CI 7.5, 11.3; 85 of 919 patients) in the enoxaparin group ($p<0.01$). A 56 percent relative risk reduction in favor of fondaparinux compared with enoxaparin was observed. The incidence of all DVT was 4 percent in the fondaparinux group and 9 percent in the enoxaparin group ($p<0.01$). The incidence of proximal DVT was 0.7 percent in the fondaparinux group and 2.5 percent in the enoxaparin group ($p<0.01$). The incidence of symptomatic pulmonary embolism was the same in the two groups (two patients in each group). Bleeding rates were comparable in the two groups.[1,27]

Treatment of DVT and PE

Recent well-designed studies confirm that fondaparinux is as effective as dalteparin for the treatment of DVT (Annals of Internal Medicine 2004;140:867). For the treatment of PE, fondaparinux is at least as effective and safe as unfractionated heparin (N Engl J Med 2003;349:1695). An earlier study evaluated the efficacy and safety of fondaparinux in comparison with dalteparin in the treatment of acute symptomatic proximal DVT in a Phase II study enrolling 453 patients. Patients were randomly assigned therapy with subcutaneous fondaparinux 5 mg, 7.5 mg, or 10 mg once daily plus a placebo injection twice daily or subcutaneous dalteparin 100 IU/kg twice daily plus a placebo injection once daily. Warfarin was started on day-1 or -2 and titrated to achieve an INR between 2 and 3. Fondaparinux or dalteparin was discontinued when the INR was maintained at 2 or greater for 2 consecutive days and the patient had received the study drug for 5 days or longer. Fondaparinux or dalteparin was continued for a mean of 6.6 to 6.9 days. The primary outcome assessment was completed in 438 patients. Comparable efficacy in the four treatment groups was observed. A positive outcome (defined as improvement by at least 2 mm in the thrombus size as assessed by ultrasound or perfusion lung scan) occurred in 46 percent of patients treated with fondaparinux 5 mg, 48 percent of patients treated with fondaparinux 7.5 mg, 42 percent of patients treated with fondaparinux 10 mg, and 49 percent of patients treated with dalteparin. Fourteen recurrent thromboembolic complications occurred: 8 (2.4 percent) in the fondaparinux-treated patients and 6 (5 percent) in the dalteparin-treated patients. Major bleeding occurred in six patients: four at the site of malignant lesions, one in the presence of an INR of 4.7, and one at the injection site in a patient treated with fondaparinux 10 mg.[18]

Other Uses

A pilot study used fondaparinux as an antithrombotic agent during percutaneous transluminal coronary angioplasty. The fondaparinux was able to inhibit thrombin generation without modification of aPTT and ACT and the rate of abrupt vessel closure was within range of rates reported in historical controls.[28]

Fondaparinux was evaluated as an adjunct to fibrinolysis in acute myocardial infarction using a randomized, open-label, dose-finding study enrolling 333 patients. Patients were treated with aspirin and alteplase and randomized to receive either unfractionated heparin intravenously for 48 to 72 hours or fondaparinux daily for 5 to 7 days. Heparin was administered as a 5,000 unit bolus prior to the alteplase followed by an infusion of 1,000 units/hour for 48 to 72 hours adjusted to a target activated partial thromboplastin time of 50 to 75 seconds. Fondaparinux was administered intravenously on the first day and subcutaneously thereafter at a low dose (4 mg or 6 mg if weight >90 kg), medium dose (8 mg or 6 mg if weight <60 kg or 10 mg if weight >90 kg), and high dose (12 mg or 10 mg if weight <60 kg). The patients had to have chest discomfort of at least 30 minutes within the last 6 hours and had at least 0.1 mV ST-segment elevation in two contiguous limb leads or $\geq$ 0.2 mV in two contiguous chest leads. Patients were excluded if there was a contraindication for thrombolytic treatment, oral anticoagulation, hemorrhagic diathesis, active peptic ulcer, history of stroke, recent major trauma or organ biopsy, blood pressure >180/110 mmHg, previous bypass surgery, recent stent deployment, renal insufficiency (SCr $\geq$1.8 mg/dL), cardiac catheterization, or use of an investigational drug within 30 days. The primary endpoint for the study was a TIMI flow grade in the infarct-related artery at 90 minutes and on days-5 to -7. Other endpoints included all-cause mortality, incidence of reinfarction and urgent revascularization. The primary safety endpoint was the incidence of intracranial hemorrhage or any bleed requiring blood transfusion. Thrombolysis in TIMI flow grade 3 rates at 90 minutes was similar in the four treatment groups. Among patients with TIMI 3 flow at 90 minutes who did not undergo a coronary intervention (155 patients), a trend toward less reocclusion of the infarct-related vessel on days-5 to -7 was observed in the fondaparinux-treated patients than the heparin-treated patients (0.9 vs 7 percent; $p=0.065$). During the 30-day follow-up period, fewer patients in the fondaparinux group required revascularization (39 percent vs 51 percent, $p=0.054$). Among patients who underwent coronary intervention at 90 minutes, clinical outcomes were similar in the fondaparinux and heparin groups. The combined incidence of intracranial hemorrhages and need for blood transfusion was the same in the fondaparinux and heparin groups. Minor bleeding occurred slightly more frequently in the fondaparinux group ($p=0.058$).[29]

Another dose-ranging study is underway evaluating four doses of fondaparinux compared with enoxaparin in 1,000 patients with acute coronary syndromes.[30]

Contraindications

Fondaparinux is contraindicated in patients with severe renal impairment (creatinine clearance < 30 mL/min), patients with body weight < 50 kg (110 pounds), and patients with active major bleeding, bacterial endocarditis, thrombocytopenia associated with a positive *in vitro* test for anti-platelet antibody in the presence of fondaparinux

sodium, or in patients with a known hypersensitivity to fondaparinux.[1]

In clinical trials the incidence of bleeding was doubled in patients weighing less than 50 kg compared to those weighing 50 kg or more (5.4 vs 2.1 percent).[1]

Warnings and Precautions

Patients anticoagulated or scheduled to be anticoagulated with fondaparinux, low molecular weight heparins, or heparinoids are at risk for the development of an epidural or spinal hematoma when epidural/spinal anesthesia or spinal puncture is utilized. This can result in long-term or permanent paralysis. The risk of hematoma formation is increased by traumatic or repeated epidural or spinal puncture, the use of indwelling epidural catheters for administration of analgesia, and the concomitant use of medications affecting hemostasis such as nonsteroidal anti-inflammatory agents, platelet inhibitors, or other anticoagulants. Patients should be frequently monitored for signs and symptoms of neurological impairment.[1]

Fondaparinux is not intended for intramuscular administration.[1]

Fondaparinux is not interchangeable with heparin, low molecular weight heparins, or heparinoids on a unit for unit or mg-to-mg basis.[1]

The risk of hemorrhage increases with decreasing renal function. Major bleeding occurred in 1.6 percent of patients with normal renal function, compared with 2.4 percent of patients with mild renal impairment, 3.8 percent of patients with moderate renal impairment, and 4.8 percent of patients with severe renal impairment. Fondaparinux is contraindicated in patients with severe renal impairment and should be used with caution in patients with moderate renal impairment (CrCl 30 to 50 mL/min). Renal function should be assessed periodically in patients receiving fondaparinux, and therapy should be discontinued immediately in patients who develop severe renal impairment or labile renal function. After discontinuation of fondaparinux, its effects may persist for 2 to 4 days in patients with normal renal function and longer in patients with renal impairment.[1]

Fondaparinux should be used with caution in patients with conditions in which the risk of bleeding is increased, such as congenital or acquired bleeding disorders, active ulceration and angiodysplastic gastrointestinal disease, hemorrhagic stroke, or shortly after brain, spinal, or ophthalmologic surgery, or in patients receiving concomitant platelet inhibitors.[1] Fondaparinux should also be used with caution in geriatric patients and patients with bleeding diathesis, uncontrolled arterial hypertension, or a history of recent gastrointestinal ulceration, diabetic retinopathy, or hemorrhage.[1] Major bleeding occurred in 1.8 percent of patients under 65 years of age, 2.2 percent of patients 65 to 74 years of age, and 2.7 percent of patients 75 years of age or older.[1] If unexpected changes in coagulation parameters or major bleeding occurs, fondaparinux should be discontinued.[1]

Thrombocytopenia may occur with fondaparinux. Moderate thrombocytopenia (platelet counts between 100,000/mm^3 and 50,000/mm^3) occurred in 2.9 percent of fondaparinux-treated patients, and severe thrombocytopenia (platelet counts less than 50,000/mm^3) occurred in 0.2 percent of patients. If the platelet count falls below 100,000/mm^3, fondaparinux should be discontinued.[1] Fondaparinux should be used with caution in patients with a history of heparin-induced thrombocytopenia.[1]

Fondaparinux is in Pregnancy Category B. Animal studies have not revealed any impaired fertility or harm to the fetus at doses up to 65 times the recommended human dose based on body surface area. It has not been studied in pregnant women; therefore, it should be used in pregnancy only if clearly needed.[1] Fondaparinux is excreted in the milk of lactating rats. It is not known if it is excreted in human milk. Caution is recommended when fondaparinux is administered to a nursing woman.[1]

The safety and effectiveness of fondaparinux in pediatric patients have not been established.[1]

Adverse Reactions

Fondaparinux has been well tolerated in clinical trials. Like other low molecular weight heparins and heparinoids, major and minor bleeding is a dose-related risk with fondaparinux therapy.[7] Overall, major bleeding occurred in 2.7 percent of fondaparinux-treated patients in clinical trials, compared to 1.9 percent of patients treated with enoxaparin. Minor bleeding occurred in 3 percent of fondaparinux-treated patients and 2.9 percent of enoxaparin-treated patients.[1]

Minor local irritation (injection site bleeding, rash, and pruritus) may occur following subcutaneous administration of fondaparinux.[1]

Thrombocytopenia was reported in the clinical trials.[1] Increases in aspartate and alanine aminotransferase levels greater than 3 times the upper limit of normal, respectively, occurred in 1.7 percent and 2.6 percent of fondaparinux-treated patients and 3.2 percent and 3.9 percent of enoxaparin-treated patients.[1]

Drug Interactions

Fondaparinux pharmacokinetics or pharmacodynamics were not altered by concomitant administration of platelet inhibitors (aspirin), NSAIDs (piroxicam), oral anticoagulants (warfarin), or digoxin.[1,16,31] Fondaparinux did not influence the pharmacodynamics of warfarin, aspirin, piroxicam, or digoxin, or the pharmacokinetics of digoxin at steady state.[1,31,32]

Bleeding parameters were not altered by concomitant administration compared to the effects produced by aspirin alone. However, concurrent therapy of aspirin and fondaparinux may enhance the antithrombotic effects of each agent or increase the risk of bleeding because of the reduction in thrombin generation and the inhibition of platelet activity.[16] It is recommended that agents that may enhance the risk of hemorrhage should be discontinued prior to fondaparinux administration. If concomitant administration is necessary, patients should be closely monitored for bleeding.[1]

Fondaparinux produced less than 30 percent inhibition of CYP2A6-mediated coumarin metabolism and had minimal effects on CYPs 1A2, 2C19, 2D6, 3A4, and 3E; therefore, fondaparinux is not expected to result in clinically important interactions mediated by inhibition of metabolism via these isozymes.[1]

Recommended Monitoring

Periodic routine complete blood counts (including platelet count), serum creatinine level, and stool occult blood tests are recommended during fondaparinux therapy.[1]

Routine coagulation tests such as the prothrombin time (PT) and activated partial thromboplastin time (aPTT) are relatively insensitive measures of fondaparinux activity and are not useful for monitoring fondaparinux therapy. The anti-Factor Xa activity of fondaparinux sodium can be measured by the use of an anti-Xa assay using fondaparinux as the calibrator.[1]

Dosing

For DVT prophylaxis post-operatively, fondaparinux is administered as a subcutaneous injection at a dose of 2.5 mg once daily for patients weighing at least 50 kg. Fondaparinux may be initiated 6 to 8 hours postoperatively, after hemostasis is achieved. The usual duration of administration is 5 to 9 days. Therapy has been continued up to 11 days.[1]

For the treatment of DVT and/or PE, the dose of fondaparinux is 5 mg subcutaneously once daily for patients weighting less than 50 kg, 7.5 mg /d for patients weighing between 50 and 100 kg, and 10 mg/d for patients weighting over 100 kg.

The ususal duration of administration is 5 to 9 days. Fondaparinux should be injected subcutaneously into fatty tissue at alternating injection sites (e.g., between the left and right anterolateral or the left and right posterolateral abdominal wall).[1]

Contraindications

Fondaparinux should be used cautiously in patients with renal impairment and is contraindicated in patients with a creatinine clearance < 30 mL/min. Prophylactic use of fondaparinux is contraindicated for patients weighing less than 50 kg. The safety of this drug has not been established in pediatric patients or pregnant women.

Product Availability

Fondaparinux received FDA approval in December 2001. It is available as a sterile, preservative-free injectable solution for subcutaneous administration in single dose, prefilled syringes containing fondaparinux 2.5 mg/0.5 mL of an isotonic solution of sodium chloride and water for injection. The pH is between 5 and 8. The syringe is affixed with a 27 gauge x 1/2 inch needle with an automatic needle protection system. Fondaparinux should be stored at room temperature.[1]

Conclusion

Fondaparinux is a selective Factor Xa inhibitor. It is effective in the prevention of thrombosis following major orthopedic surgery. It offers an alternative antithrombin therapy to the use of heparin or low molecular weight heparins in various surgical procedures. Fonadaparinux is effective for the treatment of DVT and PE. Rates of bleeding with fondaparinux and enoxaparin appear to be similar. Fondaparinux would not be expected to cause heparin-induced thrombocytopenia, and this reaction has not been reported to date. Because of its prolonged half-life and absence of a reversal agent, fondaparinux should be avoided in patients at risk for bleeding and in those with questionable renal function.

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